Coxsackie Viruses

A Review of Pathologic, Epidemiologic, Diagnostic and Etiologic Observations

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• *Coxsackie disease comprises three clinical entities—herpangina, so-called non-paralytic poliomyelitis, and epidemic pleurodynia. Several strains of antigenically-related viruses, Groups A and B, designated as Coxsackie virus have been isolated from stool specimens and from material from the throat of many patients with the diseases mentioned. Inasmuch as the virus has also been recovered from normal persons, there is as yet uncertainty as to causal relationship between the presence of the virus and the disease. Reports of the isolation of Coxsackie virus and poliomyelitis virus from the same patient make difficult the interpretation of the findings.*

The diagnosis of Coxsackie disease entails animal inoculation and serologic procedures. Emphasis is placed on the necessity of obtaining stool specimens, throat washings, and "paired" blood specimens from patients suspected of the disease.

ONE OF THE MOST recent and important observations in virology was the discovery of Coxsackie or "C" viruses by Dalldorf and Sickels in 1948.[6] Epidemiologic studies on poliomyelitis in Coxsackie, N. Y., an urban community in the Hudson River Valley, led to the observation of the new virus in stool specimens obtained from two boys with nonparalytic poliomyelitis. In Wilmington, Del., in the same year, Dalldorf noted a similar virus in stool specimens obtained from a group of patients with symptoms of atypical poliomyelitis. Approximately two years later, Melnick, Shaw, and Curnen[18] reported the isolation of the virus not only from patients, but from flies and sewage. They also described six cases of accidental laboratory infection among personnel working with the virus.

In 1950, in England, Findlay and Howard[9] observed a virus in the stools of patients with a disease entity designated, in that country, as epidemic pleurodynia or Bornholm disease. The virus has now been identified as Coxsackie virus. Another significant observation was that of Huebner, Cole, Beeman, Bell, and Peers,[12] who isolated Coxsackie virus from patients with herpangina. Thus, within a period of four years, Coxsackie viruses have been isolated from patients with three seemingly unrelated symptom complexes.

THE VIRUS

Coxsackie virus is extremely small, ranging in size from 10 to 20 millimicrons.[13, 22] It has been propagated in tissue culture[25] and in embryonated eggs.[6] It is resistant to antibiotics such as penicillin, streptomycin, and chloramphenicol. The best source of the virus is feces collected from patients early in the course of the disease. It has also been isolated from stools, from throat swabs and rectal swabs. One investigator reported observing it in spinal fluid, blood, and urine.[11]

Many strains of the virus have been noted and, on the basis of histologic examinations carried out on experimentally-infected suckling mice, two distinct groups, A and B, have been identified. Group A strains produce myositis in skeletal muscles, and Group B strains cause not only myositis but, also, encephalomyelitis, myocarditis, pancreatitis, hepatitis, and inflammatory lesions in fat pads. Reactions to complement-fixation and neutralization tests also confirm the existence of the two groups. Furthermore, there are several different types of Coxsackie virus in each group. The viruses produce paralysis in both suckling mice and hamsters, and cause a mild febrile illness in young cynomologous monkeys and in chimpanzees. Minute cytoplasmic fuchsinophilic granules have been observed in lesions produced in suckling mice.[21] Although suckling mice are most susceptible to the virus, it was noted recently that pancreatitis developed in adult mice that ate infected suckling mice.[15]

The Coxsackie viruses are widely distributed, yet overt illness is comparatively uncommon. To date, isolation of Coxsackie viruses has been reported from at least 24 states: Alabama, California, Colorado, Connecticut, Delaware, Florida, Georgia, Illinois, Louisiana, Maryland, Massachusetts, Minne-

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Presented before the Section on General Medicine at the 81st Annual Session of the California Medical Association, Los Angeles, April 27 to 30, 1952.

sota, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, Rhode Island, South Dakota, Tennessee, Texas, Virginia, Washington, Wisconsin.* The disease has been reported from England, Canada, Denmark, France, Israel, and Alaska.[1, 9, 10, 17, 24, 27]

Man is evidently the chief reservoir of infection. Recently, however, Morris and O'Connor[20] noted that the serum from wild cottontail rabbits (Sylvilagus floridanus) trapped in Maryland neutralized three strains of Group A Coxsackie viruses. The epidemiologic significance of this finding is as yet unknown. Serologic surveys in man indicate that many persons have been exposed to the infection, yet to their knowledge have not had Coxsackie disease. Such evidence indicates that inapparent infections occur, as has been noted in poliomyelitis. Although the majority of patients from whom viruses are recovered are under ten years of age[7] they have been obtained from numerous patients in the second decade of life. Dalldorf observed that the disease more often affected boys than girls, but Cole, Bell, Beeman, and Huebner[4] noted no significant difference in this regard. The disease is most prevalent in the late summer and early fall months, as is poliomyelitis.

Coxsackie disease may occur in several members of a family. Close contact is conducive to transmission of the infection. Infection may result from contact with persons who have asymptomatic cases, with persons in whom the disease is clinically apparent, or from carriers. Cole, Bell, Beeman, and Huebner[4] were able to isolate the virus from the stools of one patient with herpangina for 76 days after the onset of illness. They stated, however, that usually it cannot be recovered for more than one month after first symptoms are observed.

CLINICAL MANIFESTATIONS

The symptoms of the disease complexes vary greatly. They include those of nonparalytic poliomyelitis and aseptic meningitis; epidemic pleurodynia or Bornholm disease; and herpangina or vesicular pharyngitis (see Table 1).

Nonparalytic poliomyelitis and aseptic meningitis. After an incubation period of from one to four days patients complain of malaise, anorexia, nausea, headache, muscular pains, and weakness, especially in the legs. Stiffness of the neck is a conspicuous symptom. Temperature of from 100° to 104° F. may persist during the first week of the illness. In many instances, the illness is heralded by symptoms of infection in the upper respiratory tract. Muscle weakness occasionally can be detected. Pleocytosis in the cerebrospinal fluid is frequently observed in this form of the disease.

TABLE 1.—*Clinical Entities from Which Coxsackie Viruses Have Been Isolated*

Clinical Entity	Group A	Group B
Aseptic meningitis		+ *
Fever of unknown origin		+
Herpangina	+	
Non-paralytic poliomyelitis	+	+
Pleurodynia	+	+
Poliomyelitis	+	+
Respiratory infections	+	+
Summer grippe		+
Three-day fever	+	
Normal	+	

* +Indicates isolation of virus.

Epidemic pleurodynia (Bornholm disease). The symptoms that occur at the onset of this clinical entity are not unlike those observed in several viral diseases—namely, headache, fever of from 101° to 104° F., nausea, vomiting, pain in muscles of the extremities, backache, and stiffness of the neck.[9, 16] Sore throat is not uncommon. The striking symptoms, however, are pains in the chest and abdomen which cause severe distress in the patient and account for the designation of "devil's grippe" or epidemic pleurodynia. The term *Bornholm disease*, used by the English, derives from Bornholm Island in the Baltic Sea.

Herpangina or vesicular pharyngitis. In 1920, Zahorsky[29] described herpangina as a clinical entity of unknown cause. The disease is characterized by fever, headache, abdominal pain, and a sore throat. Early in the course of the disease the only clinically observable change in the throat is diffuse congestion. From 12 to 24 hours later, small petechiae may be noted about the fauces, and later they develop into vesicles and finally into aphthous areas. The disease usually lasts four or five days, and the patient then makes uneventful recovery. Huebner, Cole, Beeman, Bell, and Peers,[12] in 1951, reported isolation of Group A strains of Coxsackie virus in material from throat washings and rectal swabs and in the stools of 32 of 37 patients with herpangina. They noted that the disease was prevalent in the metropolitan area of the District of Columbia. The disease has since been observed by numerous physicians in other areas of the United States. Recurrence of the infection in the same patient has been reported.[4]

DIAGNOSIS

The clinical diagnosis of Coxsackie disease is difficult. It may be suspected in young children with symptoms of so-called nonparalytic poliomyelitis, especially when the outstanding symptom is stiffness of the neck. The disease may also be suspected in unexplained concurrent severe chest and abdominal

*References: 2, 3, 5, 6, 11, 14, 16, 18, 19, 23, 25.

pain. In herpangina, the presence of vesicles about the fauces is characteristic. The cardinal symptoms already mentioned are usually accompanied by headache, nausea, fever and muscular pain. A definite diagnosis, however, can be made only in the laboratory. The isolation of Coxsackie virus from the stool of a patient, or from material from the throat swabs in the case of herpangina, is diagnostic if the presence of other infectious agents causing symptoms similar to those caused by Coxsackie virus cannot be demonstrated. In addition to demonstrating the virus, a rise in titre of neutralizing antibodies or complement-fixing antibodies should be observed. The specimens required by the laboratory are: (1) A stool specimen obtained early in the course of the disease; (2) from patients with herpangina, specimens of material washed or swabbed from the throat, kept moist in a serum broth. (3) Two specimens of blood (10 ml. each), the second obtained approximately two weeks after the first.

Demonstration of the virus in stool specimens is comparatively simple. An inoculum is prepared from the specimens by making a 20 per cent suspension in distilled water. The suspension is ground in a Ten Broeck grinder, then centrifuged at 2° C. for one-half hour at 13,000 rpm. The supernate is removed and exposed for one-half hour at room temperature to 1,000 units of penicillin and 10.0 mg. of streptomycin per milliliter. Three-hundredths of a milliliter of the inoculum is injected intramuscularly, intraperitoneally, or intracerebrally into suckling mice from one to two days old. Observations are then made for paralysis of the extremities, particularly the posterior limbs. If the virus is present in the inoculum, paralysis and death usually occur within five days after inoculation. The presence of the virus is determined by histologic examination of sections of the infected mice, and by neutralization and complement-fixation tests. (A large breeding colony of mice to supply suckling mice is an essential requirement.)

Routine complement-fixation tests on serum from patients for the diagnosis of Coxsackie disease are yet impractical because of the multiplicity of strains of the virus. On the other hand, serologic tests by means of complement-fixation and neutralization procedures are useful to detect a rise in antibody titre in the serum of a patient from whom the virus has been recovered. Thus "paired" specimens of blood from patients suspected of Coxsackie disease are essential.

RELATIONSHIP OF THE VIRUS TO DISEASE

The relationship of the group of Coxsackie viruses to the diseases from which they have been isolated is not definitely known (Table 1). Cole, Bell, Beeman, and Huebner[4] expressed the opinion that herpangina is definitely caused by Group A strains of Coxsackie virus. They noted the presence of the virus in 45 of 50 cases of typical herpangina. On the other hand, they expressed belief that the presence of the virus in the stools of patients who had the other clinical diseases thought by some observers to be caused by Coxsackie viruses might be only incidental. The etiologic significance of the virus in nonparalytic poliomyelitis has been critically evaluated by several investigators, particularly by Cole, Bell, Beeman, and Huebner,[4] who noted in a survey of the literature and of their own material, that the virus was observed to be present in from 170 (9.6 per cent) of a total of 1,763 cases. The cases were classified into two groups—namely, 701 cases of poliomyelitis and 1,062 cases of nonpoliomyelitis. Coxsackie virus was present in 10.3 per cent of the cases of poliomyelitis and in 9.2 per cent of the other group, indicating no significant difference between the two groups with regard to the percentage of patients carrying the virus.

Experimental evidence that Coxsackie virus is the cause of epidemic pleurodynia was reported, however, by Findlay and Howard[9] who observed symptoms typical of Bornholm disease in an adult volunteer who was inoculated intranasally with the virus. Later, specific complement-fixing antibodies were demonstrated in serum from the patients. In addition, two groups of investigators isolated Coxsackie virus from patients in epidemic areas. Weller, Enders, Buckingham, and Finn,[28] and Lazarus, Johnston, and Galbraith[16] recovered the virus from the stools of a high percentage of patients with epidemic pleurodynia.

Inasmuch as the viruses of poliomyelitis and Coxsackie disease have been recovered from the same patient, it has been postulated that the Coxsackie viruses have a "sparing" effect on the virus of poliomyelitis. Experiments were carired out by Sulkin and Manire[26] to determine the effect of simultaneous inoculation of animals with both viruses. They observed that Coxsackie virus did not affect the course of poliomyelitis in mice, but that Lansing poliomyelitis virus favorably affected the course of Coxsackie disease in mice. Dalldorf[8] infected young mice with Group B Coxsackie virus, and then with poliomyelitis virus from four to ten days later. The animals acquired pronounced resistance to the poliomyelitis virus.

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